

## PRIMARY CARE & HEALTH SERVICES SECTION

### Original Research Article

# Opioid Use as a Predictor of Health Care Use and Pain Outcomes: Analysis of Clinical Trial Data

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Conflicts of interest: None.

Disclosures: This material is based on work supported by a Department of Veterans Affairs Health Services Research and Development (VA HSR&D) Merit Review award to Dr. Kroenke (IIR 07-119) and Career Development Award to Dr. Krebs (CDA 07-215). The sponsor had no role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the manuscript for publication.

The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government.

This work was presented in abstract form at the Society of General Internal Medicine annual meeting in Toronto, Ontario, Canada in April 2015.

### Abstract

**Objective.** To examine effects of pre-enrollment opioid use on outcomes of a 12-month collaborative pain care management trial. We hypothesized that participants with opioid use would have worse pain at baseline; use more health care services and analgesics; and have worse pain outcomes during the trial.

**Design.** Secondary analysis of randomized controlled trial data.

**Setting.** Veterans Affairs (VA) primary care.

**Subjects.** Patients age 18-65 years with chronic pain of at least moderate severity who were enrolled in a 12-month pragmatic trial of a telephone-based collaborative care intervention for chronic musculoskeletal pain.

**Methods.** Participants were categorized as opioid users ( $n = 84$ ) or non-users ( $n = 166$ ) at baseline and trial randomization was stratified by opioid use. We used logistic regression to examine cross-sectional associations with baseline opioid use and mixed-effect models for repeated measures to examine baseline opioid use as a predictor of Brief Pain Inventory (BPI) scores over 12 months.

**Results.** At baseline, 33.6% reported use of prescribed opioids. Baseline opioid users had higher baseline BPI scores and higher health-related disability than non-users. Baseline opioid users also had more outpatient visits (15.0 vs. 10.1;  $p = 0.001$ ) and received more analgesics ( $p < 0.001$ ) during the

**trial. In the final multivariable model examining effects of baseline opioid use on BPI over 12 months, opioid users and nonusers had a non-significant difference of 0.25 points ( $p=0.098$ ). In conclusion, although baseline opioid users had worse pain at baseline and used more health care during the study, response to the intervention was not significantly modified by pre-existing opioid therapy.**

**Key Words.** Chronic Pain; Opioid Analgesics; Primary Care

## Introduction

Controlled trials of long-term opioid therapy have not been published, but observational studies of patients with chronic pain have found associations of long-term opioids with worse pain outcomes, including more severe pain, functional disability, and psychological distress [1–6]. These observed associations may be attributable, in part, to clinical decisions to reserve opioid therapy for patients with higher levels of pain-related distress and for those who fail to respond to first and second-line pain treatments. However, it is also possible that treatment with opioids may contribute to persistence of pain by altering pain modulatory systems, reinforcing counterproductive pain behaviors, or interfering with participation in non-opioid therapies.

We analyzed data from a 12-month pragmatic trial of a telephone-based collaborative care intervention for primary care patients with chronic musculoskeletal pain [7]. In this paper, we examine relationships of pre-enrollment opioid use with baseline characteristics, health care service use, and pain outcomes. Our specific objectives were to 1) describe patient factors associated with pre-enrollment opioid use; 2) compare health care service and analgesic use among pre-enrollment opioid users and non-users over 12 months; and 3) examine whether pre-enrollment opioid use predicted pain outcomes or modified the intervention effect. Compared to participants without pre-enrollment opioid use, we hypothesized that participants with pre-enrollment opioid use would have worse pain and more mental health comorbidity at baseline, use more health care services and analgesics, and have worse pain outcomes in response to the active intervention.

## Methods

The Stepped Care to Optimize Pain Care Effectiveness (SCOPE) study was a 12-month pragmatic trial of a telephone-based collaborative care intervention for primary care patients with chronic musculoskeletal pain. Descriptions of the SCOPE intervention, methods, and main results have been previously published [7,8]. The study was approved by the Indiana University Institutional Review Board and VA Research Committee. All participants provided written informed consent.

## Participants and Setting

In brief, SCOPE participants were Veteran Affairs (VA) primary care patients, 18–65 years old, with musculoskeletal pain for at least 3 months and of at least moderate severity, defined as average or worst pain intensity  $\geq 5$  on a 0–10 scale. Exclusion criteria were pending pain-related disability claim, psychosis, cognitive impairment, current illicit drug use, active suicidal ideation, and life expectancy  $< 12$  months. Potentially eligible primary care patients were identified by musculoskeletal pain ICD-9 diagnoses in the VA electronic medical record and invited to participate through mail and telephone contacts. Patients who consented to participate were randomized to either the intervention or usual care. Of the 250 patients who were randomized, all provided data at baseline and 249 provided data at  $\geq 1$  follow-up time point.

## Intervention

Participants assigned to the intervention arm received 12 months of automated symptom monitoring and telephone-based care management. Automated symptom monitoring involved regular administration of a 15-item survey covering pain, mood, and medication topics by telephone interactive voice response or internet (depending on patient preference). Care management included self-management support and analgesic optimization delivered by a nurse care manager and supervised by the physician-investigator team (EEK, KK). Initial nurse care management contacts were scheduled at baseline, 4 weeks, and 12 weeks; additional calls were prompted by automated symptom monitoring alerts. The alerts were triggered by reports of inadequate pain improvement, medication non-adherence or side effects, desire to change medication, or request for contact by the nurse care manager. Analgesic optimization was guided by a stepped care medication algorithm that focused primarily on active adjustment of non-opioid medications.

## Opioid Use at Baseline

Participants were interviewed about past and current analgesic medication use at baseline and were categorized as opioid users ( $n=84$ ) or non-users ( $n=166$ ) based on their self-report of current medication use. Trial randomization was stratified by current self-reported opioid use, so equal numbers of opioid users were assigned to each trial arm (i.e.,  $n=42$  opioid users in the intervention arm and  $n=42$  opioid users in the usual care arm). We reviewed VA electronic medical records and confirmed recent prescriptions consistent with participants' self-report for 83 of 84 (98.8%) self-reported opioid users.

## Measures

Outcome assessments were administered at baseline and at 1, 3, 6, and 12 months. The primary outcome was the total score on the Brief Pain Inventory (BPI) over 12 months. The BPI is a validated pain outcome measure with demonstrated responsiveness to change

[9]. The BPI assesses pain intensity (4 items) and pain-related functional interference (7 items) on 11-point numeric rating scales [10]. Total scores range from 0-10, with higher scores indicating worse pain. Additional pain variables included location and duration of pain; pain self-efficacy measured with the Arthritis Self Efficacy Scale (ASES) [11]; and pain catastrophizing, measured with the Coping Strategies Questionnaire (CSQ) catastrophizing subscale [12,13].

Probable major depression was assessed according to the Patient Health Questionnaire 9-item depression scale (PHQ-9) diagnostic algorithm [14]. Probable posttraumatic stress disorder (PTSD) was defined as endorsement of 2 or more items on the 4-item Primary Care PTSD Screen [15] and a score of at least 41 on the 17-item Posttraumatic Stress Disorder Checklist, which has been shown to represent clinically significant posttraumatic stress [16]. Health-related disability days were determined by asking patients: "During the past 4 weeks, how many days did you cut down on the things you usually do for one-half day or more because of your physical health or emotional problems?" The number could range from 0 to 28, and high health-related disability was defined as  $\geq 14$  days. Quality of life variables were assessed with Medical Outcomes Study Short-Form 36 scales [17].

The 3-item version of the Alcohol Use Disorders Identification Test (AUDIT-C) was used to assess potentially hazardous alcohol use [18]. Substance use risk was assessed with five questions about personal history of substance use. Participants were asked about their lifetime use of 3 categories of substances: "1) medicine for pain, sleep, or nerves that was prescribed for another person; 2) marijuana; and 3) other street drugs (such as cocaine, speed, meth, heroin)". For each category, response options were the following: never, more than 10 years ago, 1-10 years ago, 3-12 months ago, and within the past 3 months. Participants were asked the following two additional questions: 1) "In your lifetime, have you ever had a problem with drugs or alcohol?" and 2) "have you ever received treatment or counseling for a drug or alcohol problem?." Participants were classified as "low risk" if answers to all 3 lifetime substance use questions were "never" or "more than 10 years ago" and answers to both personal history questions were "no."

### *Health Care Service and Analgesic Use*

Health care services and analgesic use over the 12 months of the trial were evaluated using the VA electronic medical record and pharmacy dispensing data. Health care services were quantified as numbers of outpatient visits (including primary care; specialty medicine; specialty surgery; mental health; and other types), emergency department (ED visits), and hospitalizations. Analgesic use during the trial was described in terms of "analgesic months," the sum of months of each discrete analgesic dispensed during the 12-month trial (for example, a patient on analgesic A for 6 months, analgesic B for 3 months, and analgesic C for 12 months would

have 21 analgesic months). Opioid use during the 12-month trial was described as the number of months' supply of opioids dispensed (range 0 to 12).

### *Statistical Analysis*

We used chi-square and t-tests to compare the characteristics of opioid users and non-users at baseline. To examine cross-sectional associations with baseline opioid use, we used a multivariable logistic regression model. Variables were included in the multivariable model if they were theoretically related to opioid use or associated at the  $p \leq 0.2$  level in unadjusted comparisons. To examine differences between baseline opioid users and non-users in health care service use, the number of each type of visit was compared using negative binomial regression models. Wilcoxon rank sum tests were used to compare analgesic and opioid months of opioid users versus non-users.

To examine baseline opioid use as a predictor of improvement in the BPI total score, the primary pain outcome, we used mixed-effect models for repeated measures (MMRM) with the BPI total score at 1, 3, 6, 12 months as the response variable and opioid use as the main predictor. Data were available for 248 participants at 1 month, 244 at 3 months, 245 at 6 months, and 238 at 12 months [7]. One participant did not provide any follow-up data and was excluded from this analysis. A random intercept was included to model the within-subject correlation. The first model adjusted for intervention group, BPI total score at baseline, and visit time; the second model added baseline covariates that had  $p < 0.2$  for independent association with opioid use in the baseline multivariable model (i.e., current smoking status, high health-related disability, and probable major depression). To test whether opioid use modified the intervention effect on the primary outcome, an interaction term of opioid use by treatment arm was included in the model; because no significant interaction was found, the final models did not include the interaction term.

### *Results*

Overall, participants were 83% male and had a mean age of 55.1 years (range 28-65). Self-reported race was 77% white, 19% black, and 4% other. The mean BPI total score was 5.2 at baseline. Nearly all participants reported pain duration of more than 1 year, with duration of 1-5 years in 26.4% ( $n=66$ ), 6-10 years in 19.2% ( $n=48$ ), and more than 10 years in 52.4% ( $n=131$ ).

At baseline, 84 (33.6%) participants reported use of prescribed opioids. Of participants reporting opioid use at baseline, 7 reported taking more than one opioid. When opioid and opioid-combination analgesics were categorized according to their opioid ingredient, the most common opioid was hydrocodone ( $n=65$ , 77.4% of opioid users); other opioids reported were oxycodone ( $n=15$ , 17.9% of opioid users), morphine ( $n=6$ , 7.1%), codeine ( $n=5$ , 6.0%), and fentanyl ( $n=1$ , 1.2%). At baseline, the mean number of prior analgesic medications was

**Table 1** Characteristics of participants with and without opioid use at baseline

Variable	Opioid use (n = 84)	No opioid use (n = 166)	P-value
Age in years, mean (SD)	55.2 (7.6)	55.2 (8.9)	0.97
Male, n (%)	67 (79.8)	140 (84.3)	0.37
Race, n (%)			0.36
White	68 (81.0)	124 (74.7)	
Black	12 (14.3)	36 (21.7)	
Other	4 (4.8)	6 (3.6)	
Married, n (%)	61 (72.6)	124 (74.7)	0.72
Education, n (%)			0.97
≤ High school	22 (26.2)	43 (25.9)	
Some college or trade school	43 (51.2)	83 (50.0)	
College graduate	19 (22.6)	40 (24.1)	
Employment, n (%)			0.003
Employed	44 (52.4)	116 (69.9)	
Unemployed	22 (26.2)	17 (10.2)	
Retired	18 (21.4)	33 (19.9)	
Income adequacy by self-report, n (%)			0.009
Comfortable	32 (38.1)	95 (57.2)	
Just enough to make ends meet	39 (46.4)	59 (35.5)	
Not enough to make ends meet	13 (15.5)	12 (7.2)	
Smoking, n (%)			0.022
Current	30 (35.7)	33 (19.9)	
Past	31 (36.9)	71 (42.8)	
Never	23 (27.4)	62 (37.4)	
Number of medical comorbidities, mean (SD)	2.3 (1.5)	1.9 (1.3)	0.033
High health-related disability, n (%)	45 (53.6)	35 (21.1)	<0.001
Pain variables			
BPI total score, mean (SD)	6.2 (1.4)	4.7 (1.8)	<0.001
Duration of pain in years, n (%)			0.61
≤ 5	22 (26.2)	51 (30.7)	
6-10	15 (17.9)	33 (19.9)	
> 10	47 (56.0)	82 (49.4)	
Number of pain sites, mean (SD)	5.5 (3.2)	4.6 (2.8)	0.024
ASES pain self-efficacy score, mean (SD)	5.5 (2.4)	6.6 (1.9)	<0.001
CSQ pain catastrophizing score, mean (SD)	14.5 (9.5)	9.5 (7.1)	<0.001
Mental health variables			
Probable major depression, n (%)	36 (42.9)	24 (14.5)	<0.001
Probable PTSD, n (%)	22 (26.2)	21 (12.7)	0.007
Potentially hazardous alcohol use, n (%)	19 (22.6)	43 (25.9)	0.57
Substance use risk > low, n (%)	39 (46.4)	61 (36.8)	0.14
Quality of life variables			
SF-36 general health perceptions	40.7 (29.2)	56.6 (27.5)	<0.001
SF-36 social functioning	58.6 (29.2)	70.9 (25.2)	0.001
SF-36 vitality [0-100]	34.2 (22.8)	43.8 (21.9)	0.002

ASES = Arthritis Self Efficacy Scale score (range 1–10; higher scores are better); BPI = Brief Pain Inventory (range 0–10, lower scores are better); CSQ = Coping Strategies Questionnaire catastrophizing subscale (range 0–36; lower scores are better); PTSD = Post-Traumatic Stress Disorder; SF-36 Medical Outcomes Study Short-Form 36 (range 0–100; higher scores are better).

6.9 (SD 3.0) for opioid users and 5.3 (SD 3.6) for non-users ( $p < 0.011$  for between-group comparison).

Table 1 shows unadjusted baseline comparisons between opioid users and non-users. Opioid users had worse baseline BPI total scores (6.2 vs. 4.7,  $p < 0.001$ ),

more pain sites (5.5 vs. 4.6), and more medical comorbidities (2.3 vs. 1.9,  $p = 0.024$ ) than non-users. Opioid users were less likely to be employed (52.4 vs. 69.9%,  $p = 0.003$ ), more likely to have depression (42.9 vs. 14.5%,  $p < 0.001$ ), more likely to smoke (35.7 vs. 19.9%,  $p = 0.022$ ), and more likely to have high health-related

**Table 2** Independent associations of baseline characteristics with baseline opioid use (n = 250)

Variable	OR	95% CI	P-value
Brief Pain Inventory total score	1.41	(1.11, 1.80)	0.006
High health-related disability	2.11	(1.05, 4.24)	0.036
Current smoking	1.82	(0.92, 3.60)	0.088
Probable major depression	2.06	(0.90, 4.72)	0.089
Income < comfortable	1.43	(0.76, 2.70)	0.265
Number of pain sites	1.04	(0.94, 1.16)	0.431
Unemployed	1.37	(0.58, 3.23)	0.473
Probable PTSD	0.86	(0.36, 2.09)	0.746
Number of medical comorbidities	1.03	(0.81, 1.30)	0.816
CSQ pain catastrophizing score	0.99	(0.95, 1.05)	0.817
Substance use risk > low	1.04	(0.55, 1.95)	0.907
ASES pain self-efficacy score	1.00	(0.84, 1.19)	0.975

ASES = Arthritis Self Efficacy Scale score (range 1–10; higher scores are better); BPI = Brief Pain Inventory (range 0–10, lower scores are better); CSQ = Coping Strategies Questionnaire catastrophizing subscale (range 0–36; lower scores are better); PTSD = Post-Traumatic Stress Disorder; SF-36 Medical Outcomes Study Short-Form 36 (range 0–100; higher scores are better).

disability (53.6 vs. 21.1%,  $p < 0.001$ ). [Table 2](#) shows results of the multivariable model examining baseline associations with opioid use. In this model, only baseline BPI scores and high health-related disability were independently associated with baseline opioid use. Each additional point on the BPI total score was associated with a 41% higher odds of opioid use (OR = 1.41, 95% CI: 1.11, 1.80) and high health-related disability was associated with more than twice the likelihood of opioid use (OR = 2.11, 95% CI: 1.05, 4.24).

#### Health Care Service and Analgesic Use

[Table 3](#) shows health care visits and analgesic use during the 12 month trial. Compared with opioid non-users, baseline opioid users had more outpatient visits overall (15.0 (SD 14.0) vs. 10.1 (SD 11.0);  $p = 0.001$ ), more emergency department visits (0.5 (SD 1.2) vs. 0.3 (SD 0.7);  $p = 0.042$ ), and no significant difference in the number of hospitalizations (0.1 (SD 0.3) vs. 0.03 (SD 0.2);  $p = 0.07$ ). Over the 12-month trial, baseline opioid users received more overall analgesic months (12.7 (SD 9.2) months) than non-users (4.9 (SD 4.8) months;  $p < 0.001$  for between-group comparison). Baseline opioid users also received more months of opioids during the trial than non-users (4.7 (SD 5.5) vs. 0.3 (SD 1.4) months;  $p < 0.001$  for between-group comparison).

Among participants assigned to the intervention group (n = 124), opioid users had more contacts with the nurse care manager (mean 15.5 (SD 7.3) vs. 11.3 (SD 4.5) contacts,  $p < 0.001$ ) and generated more alerts from the automated symptom monitoring system (mean 8.6 (SD 4.7) vs. 5.6 (SD 4.0) alerts,  $p = 0.001$ ) than non-users.

#### Pain Severity over 12 Months

[Table 4](#) shows unadjusted mean BPI scores at each assessment time point for the opioid use and no opioid use groups. Mean scores decreased over time in both groups, from 6.20 at baseline to 5.07 at 12 months in the opioid use group and from 4.72 at baseline to 3.61 at 12 months in the no opioid group. [Table 5](#) displays results of the multivariable models examining opioid use as a predictor of improvement in pain severity (i.e., the BPI total score) over 12 months. In this table, negative beta coefficient values indicate greater improvement in BPI over time. A test for interaction of baseline opioid use with treatment group assignment was not statistically significant ( $p = 0.95$ ), so no interaction term was included in final longitudinal models. In model 1, which controlled for baseline BPI, intervention group, and time, the difference between opioid users and non-users was a non-significant difference of 0.27 points in BPI total score over 12 months ( $p = 0.059$ ). In model 2, which additionally controlled for smoking, health-related disability, and depression, the difference between opioid users and non-users was a non-significant difference of 0.25 points on the BPI total score ( $p = 0.098$ ). In contrast, treatment group assignment, baseline BPI total score, and time were all highly significant independent predictors of the pain severity outcome (all  $p < 0.001$ ). As expected, higher baseline BPI predicted less improvement in BPI over 12 months, whereas assignment to the active intervention group and time in the study were associated with greater improvement in BPI.

#### Discussion

Consistent with our hypotheses, participants with opioid use at the time of enrollment had worse baseline pain and health-related disability at baseline and used more health services and analgesics over 12 months. Contrary to our hypothesis, baseline opioid use did not modify the intervention's positive effect on pain nor significantly predict improvement in pain outcomes over the 12 month study period.

Results of our unadjusted cross-sectional analyses are consistent with prior studies, which have reported that, among patients with pain, those treated with opioids have worse pain severity, worse quality of life, more health-related disability, more unemployment, more mental health disorders, and more tobacco use than those who are not treated with opioids [1–6]. In our multivariable baseline analysis, only baseline pain and health-related disability were independently associated with pre-enrollment opioid use. Associations with smoking and probable depression were not statistically significant in the cross-sectional multivariable model, but



**Table 3** 12-month health care service and analgesic use according to opioid use at baseline

	Opioid use (84)		No opioid use (166)		
Variable	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	P-value*
<b>Health care services</b>					
Outpatient visits, n					
Total visits	15.0 (14.0)	10 (4–23)	10.1 (11.0)	7 (4–14)	0.001
Primary care physician	2.7 (2.1)	2 (2–3)	2.2 (1.6)	2 (1–3)	0.045
Primary care other <sup>‡</sup>	0.9 (1.8)	0 (0–1)	1.0 (2.1)	1 (0–2)	0.62
Medical specialty	3.1 (4.6)	1 (0–5)	1.1 (1.8)	0 (0–1)	<0.001
Surgical specialty	1.2 (2.8)	0 (0–1)	1.0 (2.0)	0 (0–1)	0.49
Mental health	2.6 (5.3)	0 (0–3)	1.7 (4.5)	0 (0–1)	0.25
Other <sup>¶</sup>	4.4 (6.8)	1.5 (0–6)	3.0 (4.5)	1 (0–4)	0.06
ED visits, n	0.5 (1.2)	0 (0–0.5)	0.3 (0.7)	0 (0–0)	0.04
Hospitalizations, n	0.10 (0.3)	0 (0–0)	0.03 (0.2)	0 (0–0)	0.07
Hospital days, n	0.30 (1.2)	0 (0–0)	0.13 (1.0)	0 (0–0)	0.38
<b>Analgesics</b>					
Number of analgesics	3.4 (1.6)	3 (2–4)	1.7 (1.5)	1 (1–2)	<0.001
Analgesic months <sup>†</sup>	12.7 (9.2)	10 (7–18)	4.9 (4.8)	3 (1–8)	<0.001
Opioid months	4.7 (5.5)	3 (1.5–5)	0.3 (1.4)	0 (0–0)	<0.001

\*Negative binomial distribution regression analysis was used to test between-group differences for all variables, except for analgesic months, which were compared using Wilcoxon rank sum scores.

<sup>†</sup>Analgesic months is the sum of the number of months on each discrete analgesic during the 12-month trial. Opioid months is the number of months on any opioid during the 12-month trial (range 0 to 12).

<sup>‡</sup>Primary care other = non-physician visits to primary care clinics (e.g., nurse, pharmacist, nutritionist).

<sup>¶</sup>Other = non-physician visits to non-primary care clinics (e.g., nurse, pharmacist, optometrist, physical or occupational therapist, nutritionist).

ED= Emergency Department; SD= standard deviation. IQR= interquartile range (25<sup>th</sup>–75<sup>th</sup> percentile).

given the wide confidence intervals, this may have been due to our relatively small sample size.

Also consistent with prior research [4,19,20], we found that participants with opioid use at the time of enrollment used more health care services—including 50% more outpatient visits—during the 12-month trial than those without opioid use. This increased service use did not appear to be attributable to a single type of service, but rather appears relatively consistent across various types of health care services. We did not assess reasons for health care services use, so this greater use could be due to greater pain-related distress or more co-morbidity among participants with opioid use.

Mean BPI scores were higher in the opioid use group, compared with the no opioid use group, at each time point; however, the magnitude of improvement during the course of the 12-month trial was similar for both groups. In multivariable models, p-values for pre-enrollment opioid use as a predictor of pain improvement over the course of the 12-month trial were close to statistical significance (0.059 and 0.098 in the basic and fully-adjusted models). Regardless of statistical significance, the size of the difference in BPI change between users and non-users was <0.30 points on a 0–10 scale, which is unlikely to be clinically important. For context, a difference of 1.0 in BPI score has been

**Table 4** Unadjusted Brief Pain Inventory (BPI) total score among participants with and without opioid use at baseline

BPI total score, mean (SD)*	Opioid use (n = 84)	No opioid use (n = 166)
Baseline	6.20 (1.44)	4.72 (1.77)
1 month	5.52 (1.54)	4.33 (1.98)
3 months	5.50 (1.71)	4.03 (2.06)
6 months	5.27 (2.16)	3.80 (2.21)
12 months	5.07 (1.05)	3.61 (2.24)

suggested as a benchmark for minimally clinically important difference [21].

We are encouraged by our finding that patients' response to the collaborative pain management intervention was not significantly modified by pre-existing opioid therapy. Although patients on opioids were more distressed at baseline, they were still able to benefit from a relatively low-intensity telephone-based intervention involving symptom monitoring and active optimization of non-opioid analgesics. This may be because, in most cases, non-opioid analgesic options had not been exhausted prior to opioid prescribing.

**Table 5** Baseline opioid use as a predictor of improvement in Brief Pain Inventory (BPI) total score over 12 months (n = 249)\*

Variable	Model 1				Model 2			
	Beta	SE	T score	P-value	Beta	SE	T score	P-value
Opioid use	0.273	0.144	1.89	0.059	0.248	0.150	1.65	0.098
Baseline BPI total score	0.808	0.038	21.25	<0.001	0.796	0.044	18.29	<0.001
Intervention group	−0.537	0.126	−4.27	<0.001	−0.533	0.127	−4.21	<0.001
Time	−0.086	0.010	−8.72	<0.001	−0.086	0.010	−8.72	<0.001
Current smoking					0.094	0.150	0.62	0.54
High health-related disability					0.049	0.159	0.31	0.76
Probable major depression					0.041	0.167	0.24	0.81

\*Mixed-effect models for repeated measures (MMRM) with BPI total score at 1, 3, 6, 12 months as the response variable and opioid use as the main predictor. Model 1 is adjusted for intervention group (vs. control group) assignment, BPI total score at baseline (continuous), and visit time (1, 3, 6, 12 months). Model 2 is adjusted for intervention group assignment, BPI total score at baseline, visit time, current smoking (vs. past or never), high health-related disability (vs. low), and probable major depression (vs. no probable major depression).

This trial was not designed to reduce or find alternatives to opioid use. As all patients enrolling in the study had at least moderate pain on their current therapy, many study participants who were using opioids at baseline may have been non-responders to opioid therapy and potential candidates for opioid discontinuation, rotation, or tapering; however, that was not an objective of the study. There was no attempt to systematically reduce opioid use in the intervention protocol. In fact, the intervention and usual care groups did not differ in their opioid use at baseline, during, or at the end of the trial. The median daily dose in patients on opioids was 54 mg morphine-equivalent mg at both baseline and 12 months [7]. We do not know whether including opioid dose reduction or discontinuation in the intervention protocol would have altered the results of this study. Given growing evidence of harms associated with long-term and high-dose opioid therapy [22–25], future research should test the value of a similar intervention model that included an opioid dose reduction protocol.

This study has several limitations. First, this is a secondary analysis of a clinical trial that was not designed or powered to answer these research questions. This analysis was pre-planned and trial randomization was stratified by opioid use so opioid users were equally distributed between study arms. Second, the study was conducted in VA with a predominantly male sample and the mean opioid daily dose was in the moderate range; therefore, findings may not be applicable to different clinical settings or to patients receiving higher dose opioid therapy.

In summary, we found that response to a collaborative pain management intervention involving analgesic optimization was not significantly modified by pre-existing opioid therapy. Future research should examine whether a modified collaborative management protocol could be an effective strategy to achieve dual goals of improving pain outcomes and reducing intensity of opioid therapy.

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